HRF-Interacting Molecules

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Abstract: Histamine-releasing factor (HRF), also termed translationally controlled tumor protein (TCTP) and fortilin, is a highly conserved, multi-functional protein. This protein within a cell plays a critical role in the fundamental processes of cell-cycle progression, proliferation, survival, and malignant transformation. The same protein, despite the lack of signal sequence, is secreted through a nonclassical secretory pathway. The secreted protein usually termed HRF can activate IgE-primed basophils and mast cells, and works as a B cell growth factor and a chemoattractant for eosinophils. This structurally well-characterized protein interacts with many proteins to perform its intracellular and extracellular functions. This review summarizes recent studies of HRF/TCTP-interacting proteins as a major driving force to decipher its functions.

Keywords: Allergy, asthma, basophil, HRF, mast cell, proliferation, survival, TCTP.

INTRODUCTION

The search for interacting molecules is a rewarding effort to decipher the properties of a protein. Identification of the interacting proteins often provides important clues on the localization, trafficking, and function of the protein. Numerous methods have been developed for this purpose, including co-immunoprecipitation, GST (or other protein) fusion pull-down, yeast two-hybrid, and tandem affinity purification [1, 2]. With genomics-based large databases being available, combination of these methods with mass spectrometric identification of peptides is very powerful.

HRF, also termed TCTP, p21, p23, Q23, and fortilin, is a highly conserved, multi-functional protein. This protein within a cell plays a critical role in the fundamental processes of cell-cycle progression, proliferation, survival, and malignant transformation (reviewed by Bommer in this Hot Topic series). Despite the lack of signal sequence, this protein can be secreted. Historically, TCTP has been used as the term for its intracellular function, while HRF has been favored as the term for the secreted protein. TCTP/HRF exhibits amino acid sequence identities of over 40% between distantly related species [3, 4]. The 3-dimensional structures of TCTP from the yeast *Schizosaccharomyces pombe* [5], the parasite *Plasmodium knowlesi* [6], and human [7] have been solved (Fig. **1**). Fifteen of approximately 170 residues are completely or nearly completely conserved in TCTP proteins from yeast, pea, nematode, fruit fly, and mouse [3]. These invariant residues are largely clustered on one side of the β-stranded 'core' domain. The fold of this domain is similar to that of the Mss4/Dss4 family of proteins, which bind to the GDP/GTP free form of Rab proteins (members of the Ras superfamily) [5]. A flexible loop (TCTP1) and the C-terminal loop (TCTP2) following the α-helices comprise the TCTP signatures. The tubulin-binding region and the Ca^{2+}-binding area were mapped to the helical domain. A structural similarity was identified between the H2-H3 helices of TCTP and the H5-H6 helices of Bax, the part of the molecule implicated in the regulation of mitochondrial membrane permeability during apoptosis [7].

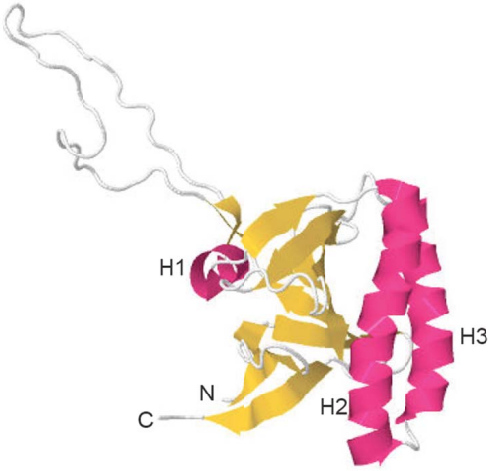

Fig. (1). Three-dimensional structure of human TCTP from as revealed by solution NMR spectroscopy. The β-stranded 'core' is similar to the fold of Mss4. TCTP-specific α-helices H1, H2, and H3 are shown. Taken from Protein Data Bank (PDB) 2HR.

TCTP CONTROLS FUNDAMENTAL PROCESSES OF GROWTH, PROLIFERATION, SURVIVAL, AND MALIGNANT TRANSFORMATION

The name "translationally controlled tumor protein" was given to this protein, because *TCTP* mRNA levels were high but the protein was not detected in Ehrlich acites tumor cells [8, 9]. TCTP is ubiquitously expressed in all tested eukaryotic cells; its expression is active in mitotically active tissues [10, 11] and subject to both transcriptional and translational

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1874-8384/12

Table 1. HRF Binding Partners

	Binding Partner	Species	Binding Site(s)		Function and Distribution	Ref.
			TCTP/HRF	Partner		
Intracellular factors						
Cell cycle Mitosis	α-tubulin	mouse	70-130	n.d.	Stabilizes microtubule. Colocalizes with microtubules in the G1, S, G2 and early M phases of cell cycle.	25
	β-tubulin	mouse	70-130	n.d.		25
	Plk	mouse human	107-172	polo box	Plk phosphorylates TCTP on S46 and S64, which is required for proper mitosis.	26
Survival / Apoptosis	p53	human	70-119	101-300	Destabilizes p53.	24
	Bcl-xL	mouse	1-40, 20IRE-D25	1-188, L90, D95	n.d. Colocalizes in cytosol and on mitochondria.	22
	calcium	human	n.d.	n.a.	n.d.	30
		rat	81-112	n.a.	n.d.	29
		human	N131, Q133, D150	n.a.	n.d. Kd= 0.022–0.025 M	27
		human mouse	1-70, E58, E60	n.a.	Intracellular Ca^{2+} scavenger, which inhibits Ca^{2+}-dependent apoptosis. Kd=10 μM. Two Ca^{2+}-binding pockets are suggested.	28
	Mcl-1	human	5-168, R21	n.d.	Mcl-1 stabilizes TCTP. Colocalize in the nucleus.	20
		mouse human	14-94	K257	Inhibits ubiqitination of Mcl-1. Colocalize partially in the cytosol.	21
	mitochondria	yeast (Mmi1)	n.d.	n.d.	n.d. Mild oxidative stress translocates Mmi1p from cytoplasm to mitochondria outer membrane.	19
		human	n.d.	n.d.	Inhibits Bax dimerization on mitochondria.	7
Protein synthesis	eEF1A	human	n.d.	n.d.	Preferentially binds GDP form of eEF1A and specifically antagonizes the eEF1Bβ-mediated guanine nucleotide exchange reaction. Partially colocalize around the nucleus.	13
	eEF1Bβ	human	n.d.	153-281		13
		human	n.d.	n.d.	n.d.	15
	eEF2	human	n.d.	n.d.	n.d.	13
	ER	human	n.d.	n.d.	n.d. Partially colocalizes with phospho disulfide isomerase (ER marker).	13
	40S ribosomal subunit	yeast (Mmi1)	n.d.	n.d.	Required for efficient translation.	14
Others	TSAP6	human	n.d.	n.d.	TSAP6 augments TCTP secretion through exosome. Colocalize around the nucleus, at the plasma membrane, and in the exosomes.	38
	Na,K-ATPase a1, a2	rat human	102-172	CD3	Suppresses Na, K-ATPase activity.	31
	NEMO	human	n.d.	n.d.	n.d.	32
	TCTP	rat	126-172	n.a.	n.d.	34
	Vit D3 receptor	human	71-132	197-427	n.d. Oxidative stress leads colocalization in the nucleus.	33
Extracellular factors						
HRF	IgE, IgG	mouse human	1-19, 107-135	Fab	Stimulate IgE-bound mast cells.	59

Ca^{2+} binding (*27-30*) and dimerization of TCTP (*34*) are also included in this table. n.d. not determined, n.a. not applicable.

control [12]. It is involved in the elongation step of protein synthesis by interacting with both eEF1A (a small GTPase) and eEF1Bβ (a guanine nucleotide exchange factor) (Table **1**) [13-15]. TCTP inhibits the latter activity, thus slowing down the elongation process, avoiding 'skipping', and resulting in more efficient elongation. G protein binding via the 'core' domain seems to be well conserved among most of TCTPs in various species. Indeed, *Drosophila* TCTP acts as the guanine nucleotide-exchange factor for Rheb (Ras homologue enriched in brain), a Ras superfamily GTPase that regulates the TSC1-TSC2-mTOR pathway [16]. Lowering Drosophila TCTP levels reduces cell size, cell number and organ size, which mimics Drosophila Rheb mutant phenotypes. Conventional TCTP KO mice are embryonic lethal [17, 18]. These *Drosophila* and mouse studies strongly implicate this protein in the regulation of growth and proliferation as well as in the control of organ size. Another conserved property of TCTP is its interaction with microtubules and mitochondria [19]. TCTP interacts with

and mitochondria [19]. TCTP interacts with Mcl-1 [20, 21] and Bcl-xL [22], anti-apoptotic members of the Bcl-2 family. TCTP stabilizes Mcl-1 through interfering with Mcl-1's degradation by the ubiquitin-dependent proteasome degradation pathway [21]. TCTP also antagonizes apoptosis by inserting into the mitochondrial membrane and inhibiting Bax dimerization [7]. RNA interference-mediated knockdown of TCTP increases the frequency of tumor reversion apparently consistent with its anti-apoptotic function [23]. By contrast, yeast TCTP displays proapoptotic activity, apparently via an interaction with the outer mitochondrial membrane [19]. A recent study identified p53 tumor suppressor as another TCTP-interacting protein [24]. Overexpression of TCTP in lung carcinoma cells reversed p53-mediated apoptosis and inhibition of TCTP expression by small interfering RNA increased apoptosis of lung carcinoma cells. Moreover, it was observed that TCTP overexpression promotes degradation of p53. Thus, TCTP acts as a negative regulator of apoptosis in lung cancer. TCTP interacts with tubulins [25]. Phosphorylation of TCTP by the protein kinase Plk decreases the microtubule-stabilizing activity of TCTP [26]. TCTP is a Ca^{2+}-binding protein [27-30] and other TCTP-interacting proteins include Na, K-ATPases [31], NEMO [32] and vitamin D_3 receptor [33] as well as itself [34].

HRF Promotes Allergic Responses

Since Thueson et al. first described an activity from cultured peripheral blood mononuclear cells that induced the release of histamine from basophils [35], histamine-releasing activities have been studied for more than 30 years [36]. In addition to several cytokines and chemokines with this activity, an unrelated protein termed histamine-releasing factor (HRF) was purified and molecularly cloned in 1995 [37] as the factor that could explain the activity found in nasal lavages, skin blister fluids, and BAL fluids during the late phase of allergic reactions [38-40]. However, it is not known whether the Thueson/Grant molecule and the molecule found in late phase reactions, are the same as this HRF. Sampson et al. showed that patients with food hypersensitivity and atopic dermatitis, but not patients with atopic dermatitis without food hypersensitivity, have higher rates of spontaneous release of histamine from basophils than normal subjects [41]. This histamine-releasing activity declined when patients avoided the offending foods for an extended period. Again, it is not known whether this interesting observation is directly related to HRF.

HRF secretion is insensitive to brefeldin A or monensin, but can be enhanced by TSAP6, a p53-inducible 5-6 transmembrane protein. HRF can be found in exosomes, suggesting that HRF is secreted through a nonclassical exosome pathway [42] (reviewed by Maeng et al. in this Hot Topic). Since human recombinant HRF can stimulate histamine release and cytokine (IL-4 and IL-13) production from IgE-sensitized basophils and mast cells [37, 43, 44], it can be considered an IgE-dependent cytokine. MacDonald et al. revealed that cell-bound IgE is required for HRF-induced basophil activation and identified functional heterogeneity among human IgE molecules: IgE from HRF-responder (HRF-R) basophils derived from ~50% of atopic patients was termed IgE+, and IgE from nonresponders (HRF-NR) was termed IgE- [45]. HRF was also isolated as a B cell growth factor [46], and can stimulate IL-8 secretion from GM-CSF-primed eosinophils [47]. More recently, HRF was shown to stimulate bronchial epithelial cells to produce IL-8 and GM-CSF [48]. Despite intensive efforts, the exact molecular basis of the IgE+/IgE- dichotomy remained an enigma for a number of years. For example, heterogeneity in the carbohydrate portion of IgE molecules failed to distinguish between IgE+ and IgE- [49]. On the other hand, the releasability of human basophils in response to anti-IgE was correlated positively with Syk tyrosine kinase levels [50-52] and negatively with SHIP (SH2 domain-containing phosphatidylinositol 5' phosphatase) levels [52]. Interestingly, HRF responses in human basophils were shown to negatively correlate with SHIP, but not Syk, levels [53], explaining some HRF-R subjects.

Limited studies on HRF-triggered signaling in human basophils have been performed. The signaling events were found to be identical or similar to those induced by anti-IgE stimulation of human basophils [54] and by antigen stimulation of IgE-sensitized mast cells: 1) stimulation with HRF was not sensitive to pertussis toxin, similar to anti-IgE/IgE-induced basophil activation. 2) Tyrosine phosphorylation of Syk was induced, and a Syk inhibitor blocked HRF-induced histamine release. A recent study also showed that loss of Syk protein was induced in HRF-stimulated human basophils, similar to anti-IgE-stimulated basophils [55]. 3) Increased intracellular Ca^{2+} and Ca^{2+}/MEK-dependent leukotriene C_4 release [56, 57] were induced by HRF in HRF-R, but not HRF-NR, basophils. 4) HRF-induced histamine release was inhibited by the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 [53], and phosphorylation of Akt, a PI3K-dependent event, was induced by HRF in HRF-R, but not HRF-NR, basophils. 5) MEK and ERK phosphorylation was induced by HRF in HRF-R, but not HRF-NR, basophils. Consistent with the many similarities in signaling between HRF-receptor and FcεRI, glucocorticoids were shown to inhibit IL-4 production from HRF-stimulated human basophils at the transcriptional level [58]. However, differences were also noted: the Vonakis *et al.* study [54] found no phosphorylation of FcεRIγ (=FcRγ) in HRF-stimulated basophils. However, this failure may be due to low levels of phosphorylation and limited cell numbers used. A pharmacological study showed that rottlerin, which inhibits protein kinase C (PKC)-δ and PKC-θ [59], enhances HRF-mediated histamine release without affecting basophil activation by either anti-IgE or antigen, although staurosporine, Bis II, Gö 6976, or pertussis toxin cannot differentiate histamine release induced by anti-IgE or antigen from that induced by HRF [60].

Most studies on this cytokine-like activity of HRF have been performed with human basophils. Therefore, its exact role in allergic disease has been elusive for two decades. For example, a clinical study failed to find a correlation between bronchial late-phase reactions to *Dermatophagoides pteronyssinus* (a house dust mite) and IgE reactivity to HRF produced from PBMCs [61]. We believe that these problems stem from three major facts in this research field: 1) the HRF receptor has not been identified, 2) functional validation using animal models of allergic disease has not been attempted, and 3) analysis of the *HRF* gene has not been performed on a large population of allergic patients.

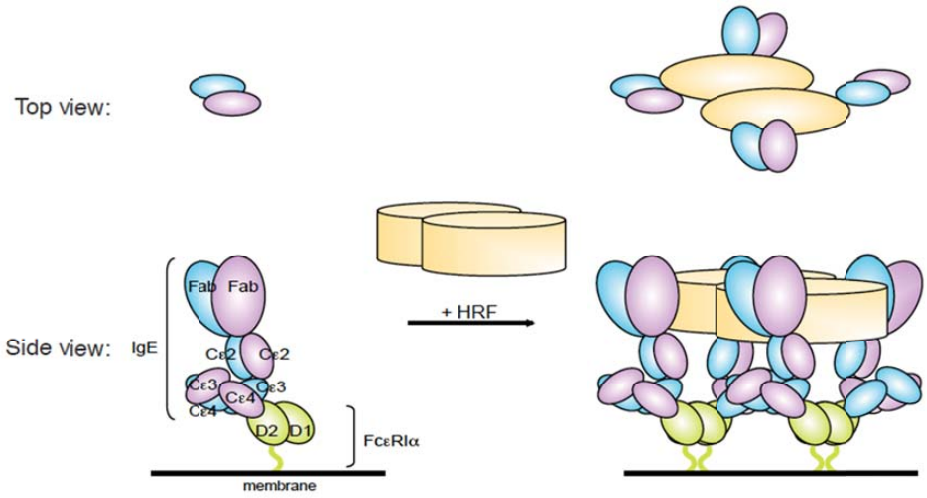

Fig. (2). Model for HRF/IgE-mediated cross-linking of FcεRI. IgE binds FcεRI α chain via the interaction between Ce3 and D2 domains. HRF can exist as a dimer and one HRF molecule can bind to two molecules of IgE *via* interactions with the N19 and H3 regions of HRF. The top view (Top) of IgE at the level of Fab and the side view (Bottom) of IgE and IgE-bound FcεRI αchain are shown on the left. After binding of an HRF dimer, four FcεRI α-nucleated complexes will be formed (Right). The cytoplasmic portion of FcεRI as well as β and γ chains of FcεRI are omitted for clarity. Taken from ref. 62.

Despite a previous study suggesting that HRF does not interact with IgE, we have recently demonstrated that a subset of IgE antibodies as well as a subset of IgG antibodies bind HRF [62]. HRF can exist as a dimer and bind to the IgE and IgG (Igs) via interactions of its N-terminal 19-residue and internal H3 regions with the Fab region of Igs (Fig. **2**). Consistent with this, HRF together with HRF-reactive IgE can activate mast cells *in vitro* and *in vivo*. Our study showed that the Ig-interacting HRF peptides, N19 and H3, which block HRF-Ig interactions can be used as specific HRF inhibitors that do not interfere with the intracellular functions of TCTP. The inhibitors can inhibit "HRF-reactive IgE"+HRF-induced mast cell activation and *in vivo* cutaneous anaphylaxis and airway inflammation [62]. Consistent with our data, transgenic mice expressing HRF/TCTP in a lung Clara cell-specific manner exhibit increased macrophages in BAL fluids in naïve mice and increased airway inflammation in OVA-sensitized and OVA-challenged mice [63]. However, the effect of HRF/TCTP overexpression in this transgenic study could not be ascribed solely to the function of the secreted HRF molecule, but the effect of the transgene could be due to the intracellular effect of HRF/TCTP as well. Intranasally administered HRF can recruit inflammatory immune cells to the lung in naïve mice in a mast cell- and Fc receptor-dependent manner [62]. These results indicate that a subset of immunoglobulins are long-sought receptors for HRF and strongly suggest that HRF has a proinflammatory role in asthma and skin immediate hypersensitivity.

FUTURE PERSPECTIVES

As exemplified as above, the search for HRF-interacting molecules has been revealing its functions. We now know a lot about the fundamental roles in cell-cycle progression, proliferation, survival, and malignant transformation. TCTP conventional knockout mice were embryonic lethal [17, 18], thus failed to provide substantial information on its function in in vivo settings. By contrast, conditional knockout mice began to churn out meaningful information: TCTP plays a modest role in thymocyte development, but it is critical for peripheral T cell maintenance and TCR-mediated cell proliferation [64]. Thus, there might be a chance to find other interacting molecules in T or other cells. Our recent study demonstrated HRF's proinflammatory role in skin anaphylaxis and airway inflammation [62]. Inhibitors of HRF-Ig interactions are being used to analyze the role of HRF in other models of allergy and other disease models, where IgE and IgG play a pathophysiological role. These inhibitors will also be useful to distinguish the roles of HRF's extracellular functions from its intracellular functions in phenomena where only its intracellular functions are assumed.

CONFLICTS OF INTEREST

None declared.

ACKNOWLEDGEMENT

None declared.

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Received: January 25, 2012 Revised: February 10, 2012 Accepted: February 17, 2012